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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,268	07/11/2005	William C. Olson	2048/59331-D-PCT-US/JPW/M	1581

23432 7590 10/05/2006

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/510,268	OLSON ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,28-31,34 and 74-79* is/are pending in the application.

4a) Of the above claim(s) *11-16,18 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 17, 19-23, and 74-79* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office acknowledges the receipt of Applicant's election and Amendment, filed on 26 May 2006. Claims 74-79 are newly added to Group I.

Election/Restriction

Applicant elects Group I, claims 1-23, with traverse. The traversal is on the grounds that there is no search burden in examining the different Inventions together. Applicant's traversal is unpersuasive for the following reasons:

There are different limitations in each Group that require a separate search. While a search of the prior art for one Group may overlap with that of another group, the searches are not co-extensive and thus would be an undue burden on Office resources.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-24, 28-31, 34, and 74-79 are pending. Claims 11-16, 18, and 33-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 26 May 2006. Claims 1-10, 17, 19-23, and 74-79 are examined to the extent that they read on the elected species.

Specification

Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

Appropriate correction is required.

Claim Objections

Claim 9 is objected to because it refers to the chemical compound by its acronym, PLG, without first identifying it by its full name, poly(lactic-co-glycolic acid).

Appropriate correction is required.

Double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-10, 20, and 75-77 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 113, 115-118, 120, and 124-126 of copending Application No. 10/489040 in view of O'Hagan *et al.* (2001).

The instant claims are drawn to a composition comprising a pharmaceutically acceptable particle and a stable HIV-1 pre-fusion envelope glycoprotein trimeric complex operably affixed thereto, each monomeric unit of the complex comprising a modified form of a gp120 of a HIV-1 isolate and a modified form of an ectodomain of gp41 of such HIV-1 isolate, wherein the modified gp120 and the modified gp41 ectodomain are bound to each other by at least one intermolecular disulfide bond between cysteine residues introduced into the modified gp120 and gp41 ectodomain.

The copending claims 113, 115-118, 120, and 124-126 of Application No. 10/489040 recite a protein comprising a first polypeptide, gp120, and a second polypeptide, gp41 ectodomain, bound to one another by a disulfide bond between the first cysteine and the second cysteine introduced by mutation into the modified gp120 and gp41 ectodomain.

O'Hagan *et al.* reviews different vaccine adjuvants including liposomes, PLG microparticles (relative dimension 100 nm-10μm), saponins, and immunostimulatory adjuvants like cytokines. See pages 71 and 76-77, Table 1 and Table 3. O'Hagan *et al.* concludes that comparative studies have indicated that microparticles are one of the

most potent adjuvants available for mucosal delivery of vaccines. See page 79, left column, 1st ¶.

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the protein of copending claims of Application No. 10/489040 such that the modified and stabilized gp120-gp41 protein is affixed to a pharmaceutically acceptable particle. One having ordinary skill in the art would have been motivated to make such a modification to enhance immunogenicity with controlled-release of entrapped antigens, as per the teachings of O'Hagan *et al.*

This is a provisional obviousness-type double patenting rejection.

Claims 3-6, 8-10, 20, and 74-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 18-20 of U.S. Patent No. 7,022,324 in view of O'Hagan *et al.* (2001) for the same reason as above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-10, 20-23, and 74-79 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barnett *et al.* (US PAT 6,602,705 B1) in view of Binley *et al.* (US PAT 7,022,324).

The instant invention is a composition comprising a pharmaceutically acceptable particle and a stable HIV-1 pre-fusion envelope glycoprotein trimeric complex operably affixed thereto, each monomeric unit of the complex comprising a modified form of a gp120 of a HIV-1 isolate and a modified form of an ectodomain of gp41 of such HIV-1 isolate, wherein the modified gp120 and the modified gp41 ectodomain are bound to each other by at least one intermolecular disulfide bond between cysteine residues introduced into the modified gp120 and gp41 ectodomain.

Barnett *et al.* describe antigen-presenting and immune-stimulating compositions that include various excipients, adjuvants, carriers, modulating agents, and the like. Barnett *et al.* specifically disclose suitable carriers such as proteins, polysaccharides, polylactic acids, polyglycollic acids, polymeric amino acids, amino acid copolymers, lipid aggregates (such as oil droplets or liposomes). Examples of particulate carriers include methacrylate polymers and PLG. Adjuvants include aluminum salts (alum), saponin, Ribi adjuvant sytem, Complete Freunds Adjuvant and Incomplete Freunds Adjuvant, cytokines such as interleukins (IL-1, IL-2, etc.), and beta chemokines (MIP, 1-alpha, 1-beta Rantes, etc.). See Abstract and column 31-32. Liposomal preparations include cationic anionic and neutral preparations. See column 47, lines 31-67. Antigens include gp120, gp41, gp160, Gag and Pol from a variety of isolates from diverse subtypes A through G and O. See column 42, lines 13-20. One embodiment of the

antigen is the HIV-1_{SF2} Env polypeptide, which can exist in both monomeric and trimeric forms. See column 57, lines 12-45. Barnett *et al.* further suggest ways to manipulate Env coding sequences to maximize gene expression: sequences encoding hypervariable regions of Env, particularly V1 and/or V2 are deleted; N-glycosylation sites are removed and/or cleavage sites are mutated. See column 58, lines 15-27.

Barnett *et al.* do not disclose an intermolecular disulfide bond between cysteine residues introduced by mutations A492C and T596C, with reference to HIV subtype B, strain JR-FL.

Binley *et al.* describe an isolated HIV-1_{JR-FL} envelope glycoprotein complex comprising a gp120 and gp41 bound to one another by a disulfide bond between a cysteine residue introduced by an A492C mutation into gp120 and a cysteine residue introduced by a T596C mutation into gp41 (¶127, ¶129, and ¶130), wherein the gp41 further comprises a mutation at the N-terminal helix, P600C (¶275). The modified gp120 further comprises a mutated furin cleavage site (¶67) and is characterized by the presence of one or more canonical glycoylation sites not present in wild type gp120, or by the absence of one or more canonical glycosylation sites present in wild type gp120 (¶114-115). PGPub'839 further teaches a trimer comprising three identical modified proteins of gp120 bound to gp41, a composition comprising an adjuvant and the HIV envelope complex or the trimer (Claims).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV Env composition of Barnett *et al.* by introducing stabilizing disulfide bond between A492C mutation into gp120 and T596C mutation into

gp41, as taught by Binley *et al.* The skilled artisan would have been motivated to do so to increase the immunogenicity of the HIV Env composition. There would have been a reasonable expectation of success, given that the stabilized trimeric gp120-gp41 complex is a better antigenic mimic of the native form and hence elicits a more relevant immune response to HIV, as taught by Binley *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Since the prior art material meets the claim limitation of PLG, the prior art PLG would necessarily have the mean diameter from about 10 nm to 100 μm. Where, as here, the Patent Office lacks the facilities to perform comparisons between the claimed material and prior art materials that reasonably appear to meet the claim limitations, the burden is properly shifted to applicant to distinguish the claimed product from the prior art product. See *In re Best, Bolton, and Shaw*, 195 USPQ 430 (CCPA 1977); *Ex Parte Gray*, 10 USPQ2nd 1922 (BPAI 1989). Absent evidence to the contrary, it appears that the sequences of US 2003/0052839 in Figure 13-15 anticipate the instantly claimed invention.

Claims 2, 17 and 19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barnett *et al.* (US PAT 6,602,705 B1) in view of Binley *et al.* (US PAT 7,022,324), and further in view of Ishikawa *et al.* (1998).

The instant invention is further limited to operably affixing the stable HIV-1 pre-fusion envelope glycoprotein trimeric complex to the particle via an agent.

The relevance of the Barnett patent and the Binley patent is set forth above. Neither discloses an agent that operably affixes the trimeric HIV-1 gp120-gp41 complex to a particle.

Ishikawa *et al.* suggest formation of immune complexes on solid phase. See abstract. Specifically, Ishikawa *et al.* describe that antibody IgGs to HIV-1 were reacted with polystyrene beads coated successively with affinity-purified (anti-2,4-dinitrophenyl group) IgG and 2,4-dinitrophenyl-HIV-1 antigen conjugates and subsequently with HIV-1 antigen-β-D-galactosidase conjugates. See Materials and Methods, p. 228-229.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Barnett by affixing the HIV-1 gp120-gp41 trimer to a particle via an IgG as taught by Ishikawa *et al.* The skilled artisan would have been motivated to do so to further stabilize the trimeric conformation of HIV-1 gp120-gp41 complex. There would have been a reasonable expectation of success, given the rapid formation of the immune complexes on the polystyrene beads, as taught by Ishikawa *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Remarks

No claim is allowable.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP §714.02 and §2163.06.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
24 September 2006

9/24/06